

ICMR GUIDELINES FOR MANAGEMENT OF TYPE 2 DIABETES 2018

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1.1 Definition

Diabetes mellitus is a syndrome of multiple etiologies characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. This disorder is often associated with long term complications, involving organs like eyes, kidneys, nerves, heart and blood vessels.

1.2 Epidemiology

In recent decades, India has witnessed a rapidly exploding epidemic of diabetes. Indeed, India today has the second largest number of people with diabetes in the world. The International Diabetes Federation (IDF) estimates that there are 72.9 million people with diabetes in India in 2017, which is projected to rise to 134.3 million by the year 2045. The prevalence of diabetes in urban India, especially in large metropolitan cities has increased from 2% in the 1970s to over 20% at present and the rural areas are also fast catching up.

1.3 Types of diabetes

According to the American Diabetes Association and the World Health Organisation, diabetes can be classified into four main types (**see Box**).

Of these, the two most important forms of diabetes are type 1 and type 2 diabetes. Type 1 diabetes is primarily due to autoimmune-mediated destruction of pancreatic beta cells, resulting in absolute insulin deficiency and thus requiring insulin for good health and survival. While type 1 diabetes is also on the increase, the actual numbers of people with type 1 diabetes in India is, relatively speaking, still small. Type 2 diabetes, on the other hand, accounts for over 90-95% of all people with diabetes and is characterized by insulin resistance and/or abnormal insulin secretion,

either of which may predominate. The diabetes epidemic relates particularly to type 2 diabetes, and predominantly due to the changing lifestyles, urbanization, demography and increased longevity.

Classification of Diabetes

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes
- Other types of diabetes (Monogenic diabetes, pancreatic diabetes, drug-induced diabetes etc.)

1.4 Differentiating Between Type 1 and Type 2 Diabetes

Table 1.1 below provides a few clinical points to differentiate between type 1 and type 2 diabetes.

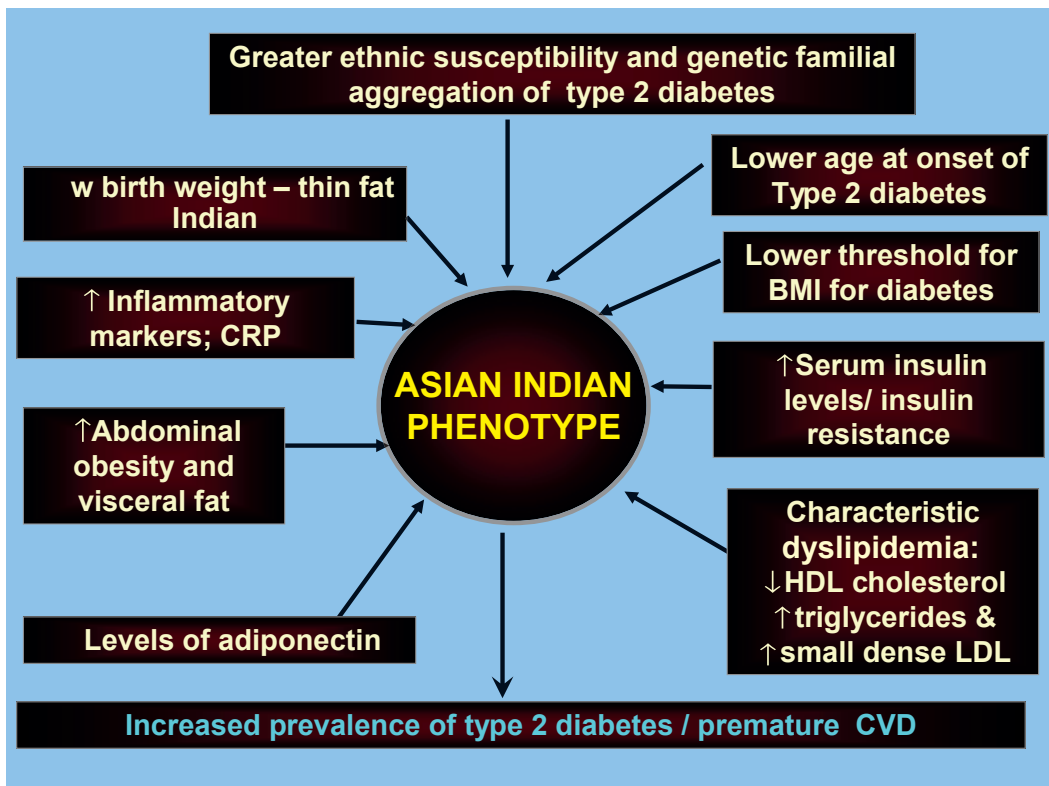
Table 1.1 Points to differentiate between type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Age at diagnosis	Usually childhood and adolescence, but can occur in adults as well	Usually postpubertal; most common in middle to later age groups
Diabetes in 1 st degree relative	Unusual	Common
Severe osmotic symptoms/ Ketosis at diagnosis	Can occur	Rare
Markers of insulin resistance	Absent	Present
C-peptide assay	Absence of beta-cell reserve	Preserved beta-cell reserve
Pancreatic autoantibodies	Present	Absent

Type 1 diabetes will not be discussed further in these guidelines and they pertain chiefly to type 2 diabetes.

Type 2 diabetes is a metabolic-cum-vascular syndrome characterized by predominant insulin resistance with varying degrees of insulin secretory defect. It is a progressive disease often associated with central obesity, dyslipidaemia and hypertension. It is more common in overweight and obese individuals of middle to late age but is increasingly being seen in younger age groups and in those with lower BMI as well. The “Asian Indian phenotype” refers to a peculiar constellation of abnormalities in south Asians, whereby for any given level of body-mass index, they tend to have higher total body fat, visceral fat, insulin resistance and prevalence of diabetes compared to white Caucasians (**Figure 1.1**).

Figure 1.1: The “Asian Indian phenotype”



1.5 Goals for management

- Glycemic control and prevention of acute complications.
- Relief from symptoms of diabetes and improvement in quality of life.
- Identification and management of comorbid conditions like obesity, hypertension and dyslipidaemia
- Prevention of microvascular complications like retinopathy, neuropathy and nephropathy.
- Prevention of macro-vascular complications like cardiovascular, cerebrovascular and peripheral vascular disease.
- Prevention of infections.

Therefore, the complete treatment of people with diabetes requires advocating a healthy life style with focus on increased physical activity and a proper balanced diet in addition to prescribing medications.

1.6 Diabetes Education

Diabetes education means empowering people with diabetes with knowledge and providing tools crucial for making them active partners in the diabetes management team. These include:

- In-depth information about diabetes, its complications and treatment
- Appropriate self care skills
- Appropriate resources for self care
- A positive attitude
- Self monitoring skills

The compliance of people with diabetes is essential for effective management of diabetes. Education programmes are intended to help people to understand why these actions are so important and thereby increase their motivation for self-management.

1.7 Prevention of Diabetes

There is an urgent need for strategies to prevent or at least slow down the emerging epidemic of diabetes apart from treating diabetes and associated complications. Several factors are thought to contribute towards the acceleration of the epidemic, the most important being the rapid epidemiological transition due to urbanization and life style changes. Identifying individuals at risk is essential in planning preventive measures. Prevention of diabetes has several windows of opportunities (**Figure 1.3**). The three stages of prevention are:

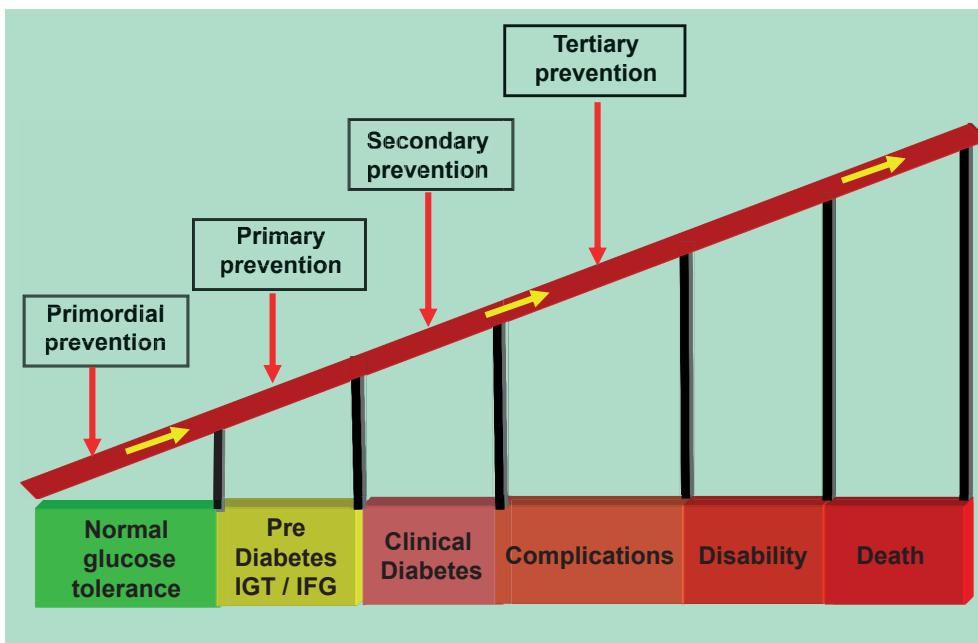
1.7.1 Primordial prevention attempts to reduce the risk factors for diabetes, e.g., reducing or preventing obesity to reduce the future risk of diabetes.

1.7.2 Primary prevention targets people who are in the stage of prediabetes to prevent the onset of diabetes. All people with prediabetes should be regularly screened and encouraged at each health care visit to pursue a healthy life-style, including a healthy diet, adequate exercise and weight control in order to prevent diabetes.

1.7.3 Secondary prevention is to prevent the onset of complications in those who are already diagnosed to have diabetes. This can be achieved by meticulous control of diabetes with the help of diet, physical activity, life style modification and antihyperglycaemic drugs as indicated.

1.7.4 Tertiary prevention of diabetes is aimed at limiting physical disability and rehabilitation measures in those who have already developed diabetic complications and preventing them from going into end stage complications of diabetes.

Figure 1.2: Levels of prevention of diabetes



Type 2 diabetes occurs at a much earlier age (at least a decade earlier) in Indians compared to other major ethnic groups. Screening of asymptomatic individuals allows diagnosis of diabetes and prediabetes to be made at an earlier stage and thus appropriate management can be instituted. In addition, it provides an opportunity for screening of cardiovascular disease (CVD) risk factors and the institution of interventions for their control.

2.1 Whom and when to screen?

Screening should be performed in all individuals >30 years of age. It should be carried out at an earlier age in adults who have one or more of the following risk factors:

- Family history of diabetes
- Overweight/obese (BMI ≥ 23 kg/m²) or have increased waist circumference (>90 cm males, >80 cm females)
- History of hypertension ($\geq 130/80$ mmHg) or on treatment for hypertension
- History of dyslipidaemia
- Sedentary physical activity
- History of gestational diabetes or macrosomia (birth weight > 3.5 kg)
- History of CVD (ischaemic heart disease, cerebrovascular disease)
- History of polycystic ovarian syndrome and/or acanthosis nigricans

2.2 How to screen?

Screening can be done by fasting plasma glucose, an oral glucose tolerance test (OGTT) using 75 gm glucose or a random plasma glucose. Glycosylated (glycated) haemoglobin (HbA1c) is also recommended for screening; however, in India there are some limitations regarding its use.

2.3 Where to screen?

Preferably, screening should be done in a health care setting. Alternatively, community screening can also be done.

2.4 Retesting:

Retesting should be done after 3 years in case of normal glucose tolerance. In case of prediabetes, it should be done annually.

2.5 Other aspects:

CVD risk factors should be identified and treated.

3.1 Diagnostic Criteria for Diabetes

- Symptoms of diabetes (see box) plus casual or random plasma glucose ≥ 200 mg/dl (Casual means without regard to time of last meal)
- Fasting plasma glucose ≥ 126 mg/dl
- 2 hour post 75 g glucose ≥ 200 mg/dl (as part of OGTT)
- Glycated Haemoglobin $\geq 6.5\%$

Any one positive test should be confirmed with another test subsequently.

3.2 Symptoms of Diabetes

- Osmotic symptoms- polyuria, polydipsia
- Weight loss in spite of polyphagia
- Tiredness, weakness
- Generalised pruritus
- Recurrent urogenital infections
- Delayed healing of wounds

More than half of all patients with diabetes will have no symptoms at all.

3.3 Criteria for the Diagnosis of Prediabetes

The term “prediabetes” refers to a situation where the blood glucose levels are higher than normal, but not high enough to warrant a diagnosis of diabetes. Prediabetes consists of two entities viz. impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The diagnostic criteria for diabetes and prediabetes are summarized in **Table 3.1**

Table 3.1: Diagnostic criteria for diabetes and prediabetes

Parameter	Normoglycemia	Prediabetes	Diabetes
FPG	< 110 mg/dl	110-125 mg/dl (IFG)	≥126 mg/dl
2-h PG	<140 mg/dl	140-199 mg/dl (IGT)	≥ 200 mg/dl
HbA1c	<5.7%	5.7-6.4%	≥ 6.5%
Random plasma glucose*			≥ 200 mg/dl (with symptoms of diabetes)

* Individuals with random plasma glucose between 140-199mg/dl are recommended to undergo OGTT
 IFG - Impaired Fasting Glucose; IGT - Impaired Glucose tolerance; FPG - Fasting Plasma Glucose; 2-h PG-2 hour post load Glucose test (oral glucose tolerance test) plasma glucose.
 HbA1c – Glycosylated Haemoglobin

3.4 Oral Glucose Tolerance Test (OGTT)

- Person to be tested should be on a normal diet (with at least 200 g carbohydrate/day) for at least 3 days before the test.
- The test should be done after an overnight fast of 8-10 hours and comprises of two blood samples: fasting and 2 hours after glucose load.
- Following the collection of the fasting blood sample for analysis of plasma glucose, the individual should be administered 75 g of glucose (1.75 g/ kg body weight for children to a maximum of 75 g) dissolved in at least 250 ml of water. The glucose load should be drunk within a period of 5 minutes.

The second sample should be collected 2 hours after the glucose load is given. The subject should be resting and refrain from smoking in between the two sample collections.

3.5 Testing for Type 2 Diabetes in Children and Adolescents

Children and adolescents aged 18 years and below should be screened for diabetes if they are overweight (weight >120% of ideal body weight) and have any of the following risk factors:

- Family history of type 2 diabetes in first degree relatives
- Signs of insulin resistance (Acanthosis nigricans)
- Hypertension
- Dyslipidaemia
- PCOS.

Any target is only a general guideline, and individualized targets are to be established. Tight glycemic control is essential in the early stages of diabetes, especially in the young to prevent complications. With the onset of complications and in the elderly, targets need to be revised based on the condition of the patient.

4.1 Targets for metabolic control in diabetes

Blood glucose, blood pressure, BMI, waist circumference and lipid targets for a patient with diabetes are listed in **Table 4.1** and **Table 4.2** below.

Table 4.1: Targets for metabolic control in diabetes

	Ideal	Satisfactory	Unsatisfactory
Fasting Plasma Glucose (mg/dl)	80 -110	111 - 125	> 125
2 hour Postprandial Glucose (mg/dl)	120 - 140	141 - 180	> 180
Blood pressure (mm Hg)	< 130/80	< 140/90	> 140/90
Body Mass Index (kg/m ²)	20 - 23	23.1 - 25	> 25
Waist (cms)	Men < 90		
	Women < 80		
Glycated Haemoglobin [HbA1c] (%)	< 7		

Table 4.2 Targets for lipid control in diabetes

Total Cholesterol (mg/dl)	< 200
HDL Cholesterol (mg/dl)	> 40 for men > 50 for women
LDL Cholesterol (mg/dl)	< 100*
Non-HDL Cholesterol(mg/dl)	<130
Triglycerides (mg/dl)	<150

*For those at high risk (established CVD, smoking, obesity, hypertension, family history of premature CVD and evidence of other vascular disease), LDL cholesterol <70mg/dl is recommended

4.2. Glycemic targets during pregnancy

Tight glycemic control is most essential during pregnancy. Glycemic targets during pregnancy are presented in **Table 4.3**.

Table 4.3: Glycemic targets during pregnancy

	Ideal
Fasting Plasma Glucose (mg/dl)	<90
1 hour Postprandial Glucose (mg/dl)	<140
2 hour Postprandial Glucose (mg/dl)	<120

Physician may request for either for a 1 hour or 2 hour postprandial blood glucose value for purposes of monitoring.

SECTION 5 MONITORING AND FOLLOW UP OF PEOPLE WITH DIABETES

5.1 How to Monitor and Follow up People with Diabetes?

- Blood glucose - FPG and 2 hr PPPG at least once a month and more often if values are not in the ideal target range.
- HbA1c at least every 6-12 months and more often (every 3 months) if values are not in the ideal target range, or tight control is being attempted
- Clinical examination needs to be done during every visit--- minimum every 3 months.
- Screening for long term complications like retinopathy, nephropathy, neuropathy, peripheral vascular disease (PVD) and coronary artery disease (CAD) at least once a year, more often if needed (see Section 8)
- Optimizing weight, waist, blood pressure, lipids.
- Routine examination of foot to be done during every visit & education regarding foot care to be given to patients in each visit
- Discourage tobacco use and excess use of alcohol

Urine glucose monitoring is not recommended. Urine examination for estimation of ketones should be done if blood glucose is greater than 400 mg/dl.

5.2 Self Monitoring of Blood Glucose (SMBG) with Glucose Monitor

It is indicated in the following conditions:

- Ideal for every patient to achieve better control of diabetes.
- All people with diabetes on insulin.
- Brittle diabetes
- Those prone to ketosis/recurrent hypoglycaemia.
- Hypoglycaemia unawareness.

- Whenever tight control is indicated — pregnancy, acute illness and complications.
- Frequency of SMBG should be individualised (e.g. with greater frequency in pregnancy).

5.3 What to do during Annual Check-Up?

- Basic clinical exam including detailed foot exam with palpation of dorsalis pedis and posterior tibial pulses, monofilament and vibration perception testing (VPT) (See Section 8)
- Retinal check-up/ fundus examination
- Blood urea / serum creatinine
- Urine — protein/albumin, micro-albuminuria if available or at least Urinary Albumin by dipstick
- ECG
- Lipids
- Hemogram
- Urine routine
- SGOT / SGPT
- Diet/ exercise to be reinforced
- Psychological support whenever necessary
- Tests to be carried out when indicated: X Ray chest, uric acid, TSH, SGOT, SGPT, vitamin B12, electrolytes, ultrasound abdomen

Advanced monitoring can be done if required in case of recurrent hypoglycaemia, severe fluctuations in blood glucose, disparity in measured glucose values and HbA1c, severe anaemia, haemoglobinopathy, hypoglycaemia unawareness etc. Here Continuous Glucose Monitoring (CGM) for 5-7 days or iSCGM (intermittently scanned CGM) for 14 days may be used.

6.1. Lifestyle Goals in Diabetes:

- To improve health through optimum nutrition
- To provide energy for reasonable body weight , normal growth and development
- To maintain glycemic control
- To achieve optimum blood lipid levels
- To individualise the diet according to complications and co-morbidities
- Achieve optimal physical activity
- Advise other behavioural changes for: smoking, other tobacco products and alcohol
- Advocate stress management

6.2 Medical Nutrition Therapy (MNT) for diabetes mellitus requires application of nutritional and behavioral sciences along with physical activity.

We need a four-pronged approach:

- Nutritional assessment which includes metabolic, nutritional and life style parameters.
- Setting goals – practical, achievable and acceptable to the patient-- individualised
- Nutritional Intervention, including nutrition education – individualized meal plans according to family eating patterns
- Evaluation – to assess if the goals have been achieved and to make necessary changes.

Based on factors like age, sex, physical activity, height, weight, body mass index

(BMI) and cultural factors, the diet is planned. The diet should be individualized, close to the family pattern, flexible, should have variety and meal timing should be according to the patient's daily schedule.

6.2.1 Dietary Recommendations:

(i) Energy:

Sufficient to attain or maintain a reasonable body weight for adults, normal growth and development for children and adolescents, to meet the increased needs during pregnancy and lactation and recovery from illness. Daily physical activity and exercise needs to be considered.

Ideal Body Weight (IBW) = (Height in cm – 100) * 0.9.

Approximately, 25 kcals/kg ideal body weight/day can be given to a moderately active patient with diabetes. The change in the daily calorie should be a gradual process, and not more than 500 calories/day.

(ii) Energy or Calorie Distribution:

(a) Carbohydrates:

Evidence is inconclusive for an ideal amount of carbohydrate intake for people with diabetes. Therefore, collaborative goals should be developed for individuals with diabetes. 55-60 % of energy from carbohydrates is an ideal recommendation. Carbohydrates should be complex in nature. Although different carbohydrates produce different glycemic responses, from clinical point of view it is important to manage total carbohydrate. It is recommended that carbohydrates from foods high in fibre e.g. whole grains (unpolished cereals and millets), legumes, peas, beans, oats, barley and some fruits with low glycemic index and glycemic load are consumed. All patients with diabetes should be encouraged to take 6 small meals a day. Food exchange system can be followed to give more variety and individualization to the diet plan.

(a) Fibre:

Fibre recommendation for general population is 40 g/day (2000 Kcals).

Traditional Indian diets that include whole grains along with whole pulses like grams, soy, green leafy vegetables and some fruits is the recommendation. Fruits like papaya, guava, apples, pears, oranges, mosambi can be taken in moderation. All fruit juices are best avoided.

(b) Proteins:

Proteins should provide 12-15 % of the total energy intake for people with diabetes – similar to the recommendations for the general population.

Proteins from vegetable sources like pulses, soy, grams, peas, low fat milk, low fat curds, fish and lean meats are recommended.

Supplementation of foods like cereal and pulse (4:1 ratio) can improve the protein quality and also gives satiety. For e.g; Idli, dosa, Missi roti, Khichdi, Dhokla, Khandvi etc.

(c) Fats:

Fats should provide 20-30 % of total energy intake for people with diabetes.

Evidence is inconclusive for an ideal amount of total fat intake for people with diabetes, therefore, goals should be individualized. Fat quality is as important as the quantity.

Fat quality

- Saturated fats (SFA) \leq 10% energy and 7% in those with raised blood lipid levels
- Polyunsaturated fats (PUFA) 10 % energy, n6: 3-7% energy, n3: $>$ 1% energy, n6/n3 ratio 5-10

- Monounsaturated Fatty Acids (MUFA) 10-15% energy + any calories left from the carbohydrate portion
- Trans fats < 1% energy – preferably totally avoided

In people with type 2 diabetes, MUFA-rich cooking oil and nuts in moderation may benefit glycemic control and CVD risk factors. This can therefore be recommended as an effective alternative to a lower-fat, higher-carbohydrate eating pattern. Use of MUFA rich oils like mustard, rice bran, peanut (groundnut) and gingelly are good options. Oils rich in n6 PUFA like safflower, sunflower, cotton seed, should be mixed with oils rich in n3 like soy and mustard to maintain N6:N3 ratio between 5-10. Use of mixed oils or alternating of oils is recommended.

(iii) Salt:

Sodium intake recommendations for people with diabetes are the same as that for the general population. Added (iodized) salt should be less than 5 g/day. For persons with hypertension and diabetes, the intake should be reduced to less than 3 g/ day. In hypertensive patients or edematous patients with nephropathy, sodium restriction is required. All preserved and processed foods such as pickles, chutneys, packaged namkeens/savouries, sauces should be restricted.

(iv) Alcohol:

It is best to avoid alcohol, however if used, should be taken in moderation. If alcohol is consumed, it should not be counted as part of the meal plan. However, it should be borne in mind that alcohol does provide calories (7 kcal/ g), which are considered as “empty calories”. In the fasting state, alcohol may produce hypoglycaemia. Alcohol can further exacerbate fatty liver, neuropathy, dyslipidaemia, obesity and also worsen blood glucose levels.

(v) Sweeteners:

Nutritive Sweeteners : These include fructose, honey, corn syrup, molasses, fruit juice or fruit juice concentrates dextrose, maltose, mannitol, sorbitol and xylitol.. All these are best avoided.

Non-nutritive Sweeteners : Aspartame, acesulfame K, stevia, sucralose and saccharin are currently approved for use. However, they should be used in moderation and are best avoided in pregnancy.

6.2.2 Dietary modifications in the presence of complications of diabetes:

(i) Nephropathy:

(a) Protein : The recommended protein intake for diabetic nephropathy patients is 0.6 g/kg of the ideal body weight plus 24 hour urinary protein loss, if this is significant. However, it is recommended that the protein intake should not be less than 40 g/ day. For patients with increased creatinine, protein restriction should be advised in consultation with the nephrologist.

(b) Sodium: It could vary from 1000 mg to 2000 mg/day depending upon the fluid status and serum sodium levels.

(c) Potassium: Potassium restriction may be required depending upon the potassium values in the blood and type of diuretic being used.

(ii) Cardiovascular Disease:

(a) Maintaining an optimal body weight and restricting salt. Use of fruits and vegetables should be encouraged, with good quality fats in moderation.

(b) Dyslipidaemia : Saturated and trans fats food sources like *vanaspati*, butter, ghee, margarine, coconut oil, red meats like sausages, ham, bacon, egg yellow, whole milk and its products should be restricted. Use of healthy oils and fibre rich foods is

recommended. Vegetarians can take flax seeds (10 g / day) in their diet as both fish and flax seeds are rich in omega-3 fatty acids which is protective for heart disease. Alcohol restriction will bring down the triglycerides. Dietary management should be accompanied with regular physical activity and exercise regimen.

6.2.3 Special situations requiring dietary modification:

(i) Sick Days

In the event of fever or other illness, the diabetic diet should be modified by changing the consistency and texture of foods to maintain adequate calorie intake. Semi solid foods and fluids or items like thin soups, milk, buttermilk, or fresh lime juice should be encouraged.

6.2.4 Lifestyle Management:

(i) Tobacco:

Smoking and tobacco chewing is totally prohibited.

(ii) Stress:

Stress management is essential which could take the form of meditation, yoga, a long outdoor walk, exercise and trying out hobbies like reading, gardening, painting etc. Practice of yoga is our traditional Indian system, which has therapeutic value in controlling our physical and mental health. It should be done under the guidance of an expert.

6.3 Physical Activity and Exercise:

Regular physical activity along with regulated exercise is an essential component of management of type 2 diabetes. Complete evaluation of patients with diabetes should be performed before recommending an exercise program. The exercise programme has to be individualized according to one's ability and individual capacity.

Benefits of exercise

- Improves insulin sensitivity, reduces the risk of heart disease, high blood pressure, bone diseases, and unhealthy weight gain
- Keeps one flexible and agile
- Helps relieve stress, anxiety and prevents depression
- Increases strength and stamina
- Promotes sound sleep
- Increases metabolic rate and digestion
- Delays the process of aging

Recommendation is about 150 minutes of aerobic activity or its equivalent /week along with some resistance training at least twice a week and flexibility exercises.

People with diabetes need an extra quick acting carbohydrate snack before the exercise and during the exercise, if the exercise period extends the daily-recommended routine.

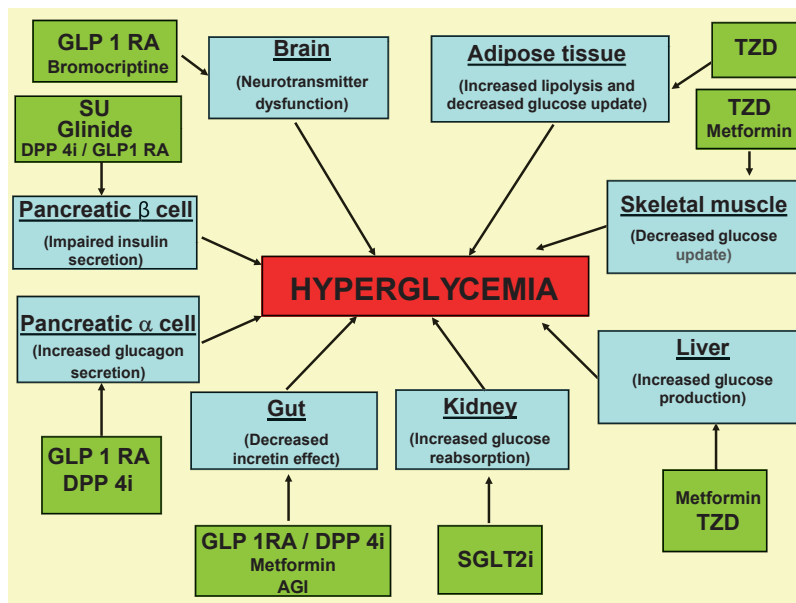
This section is divided into

1. Oral anti-hyperglycaemic drugs
2. Insulin therapy
3. Non-insulin injectable therapy

7.1 Anti-Hyperglycaemic Drugs

Blood glucose levels are determined by several factors such as absorption of glucose from gut, uptake of glucose by peripheral tissues (muscle, adipose tissue), hepatic glucose output, and secretion of hormones such as insulin and glucagon from the pancreas and incretins from the gut, as well as renal handling of glucose. Various anti-hyperglycaemic agents act by modifying the factors aiding in the control of hyperglycaemia as shown in **Figure 7.1**. The oral anti-hyperglycaemic agents currently available in India are listed in **Table 7.1**.

Figure 7.1: Mechanism of action of anti-hyperglycaemic drugs



Only the major pathophysiology at each site is depicted

Legend: SU- Sulphonylureas; DPP4i- Dipeptidyl peptidase-4 inhibitors (Gliptins); GLP-1RA- Glucagon-like peptide-1 receptor agonists; TZD- Thiazolidinediones (Glitazones); AGI- Alpha-glucosidase inhibitor; Glinide- Non-sulphonylurea insulin secretagogue (Repaglinide and Nateglinide); SGLT2i- Sodium-glucose cotransporter-2 inhibitor

Table 7.1: Oral anti-hyperglycaemic agents currently available in India

BIGUANIDES

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Metformin	250 - 2500	1 - 3	4 - 8	Urine
Metformin SR	500 – 2500	1 - 2	18-24	Urine

SULPHONYLUREAS

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Glibenclamide	2.5 -20	1 -2	16 - 24	Urine (50%) Bile (50%)
Glipizide	2.5 - 20	1 - 3	8 - 12	Urine (80%) Bile (20%)
Glipizide modified release	5 - 20	1	24	Urine (80%) Bile (20%)
Gliclazide	80 - 320	1 - 2	8 - 12	Urine (80%) Bile (20%)
Gliclazide modified release	30 - 120	1	24	Urine (80%) Bile (20%)
Glimepiride	1 - 8	1	16 - 24	Urine (60%) Bile (40%)

Newer agents like Glimepiride and Gliclazide are preferred nowadays.

DPP - 4 INHIBITORS

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Sitagliptin	25-100	1	24	Urine (87%), Faeces (13%)
Vildagliptin	25-50	1 - 2	3-12	Urine (85%), Faeces (15%)
Saxagliptin	2.5 - 5	1	2.5*	Renal (24 - 75%) and remaining hepatic excretion
Linagliptin	5	1	24	Entero-hepatic excretion
<i>Teneligliptin</i>	20 – 40	1	24	Faeces (46.5%), Renal (45%)
Gemigliptin	50	1	18 - 24	Urine (63.4%) Faeces (27.1%)

* Active metabolite acts for up to 24 hours

THIAZOLIDINEDIONES (GLITAZONES)

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Pioglitazone	7.5 - 30	1	16 - 24	Urine (15 - 30%), remaining in faeces

SGLT 2 Inhibitors

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Canagliflozin	100 - 300	1	24	Urine (33%), Faeces (41.5 %)
Dapagliflozin	5 - 10	1	24	Urine (75%), Faeces (15%)
Empagliflozin	10 - 25	1	24	Urine (54.4%), Faeces (41.2%)

ALPHA GLUCOSIDASE INHIBITORS

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Acarbose	25 - 150	1 - 3	2	Renal (2%) and rest metabolised
Voglibose	0.2 - 0.9	1- 3	1 - 1.5	Urine (5%), Faeces (95%)
Miglitol	25 - 150	1 - 3	2 - 3	Renal (95%)

Non-sulphonylurea Secretagogues (Glinides)

Drug name	Daily dosage range (min-max) (mg)	Frequency per day	Duration of action (hrs)	Predominant mode of excretion
Repaglinide	0.5 - 6	3	1	Faeces (90%), Renal (8%)
Nateglinide	60 – 360	3	1.5	Urine (83%), Faeces (10%)

In addition, various fixed dose combinations are also available although the Drug Controller of India (DCGI) does not favour fixed combination doses particularly those consisting of more than two drugs.

7.1.1 Biguanides:

Metformin is the only biguanide available in clinical practice. It mediates its effect by enhancing sensitivity of the liver and peripheral tissues to circulating insulin. The recommended starting daily dose is 500 mg after meals, which may be increased by 500 mg every two weeks until desired therapeutic goals are achieved or maximum daily doses (2500 mg) are reached. It can be used in combination with any other oral or injectable anti-hyperglycaemic agents. Metformin rarely produces hypoglycaemia when used as monotherapy. It is also associated with weight loss and is hence recommended as the first line treatment in type 2 diabetes. Metformin has a favorable effect on lipids by decreasing triglycerides. It is advisable to stop metformin at least 24 hours before elective major surgery or use of radiocontrast media. Metformin should be withdrawn if any contraindications to its use occur.

(a) Side effects:

- Gastrointestinal side effects like abdominal discomfort and diarrhoea may occur in some patients. These can be minimized if metformin is administered after meals with slow titration of doses and with the use of sustained release preparations.
- Lactic acidosis is a rare side effect and is very uncommon unless metformin is given in the presence of contraindications, given below.
- Prolonged use of metformin may be associated with vitamin B12 deficiency.

(b) Contraindications:

- Renal insufficiency (see Box)
- Hepatic insufficiency
- Respiratory insufficiency
- Hypoxemic conditions
- Acute myocardial infarction
- Congestive cardiac failure

- Alcohol abuse
- Ketoacidosis
- Severe infections

METFORMIN IN RENAL INSUFFICIENCY

The dose of metformin needs adjustment based on the patient's renal function, as assessed by the estimated glomerular filtration rate (eGFR). Metformin can be given in full doses if the eGFR is above 60 ml/min. If the eGFR is between 45 and 60 ml/min, the drug can be continued at full dose with more frequent monitoring of renal function. Below 45 ml/min, the dose should be halved and no patient started anew on metformin; the drug should be stopped if the eGFR drops below 30 ml/min.

7.1.2 Sulphonylureas:

The sulphonylureas (glibenclamide, glipizide, gliclazide and glimepiride) bind to specific sulphonylurea receptors on pancreatic β -cells and increase insulin secretion. Therapy should be initiated with the lowest effective dose and titrated upwards every two weeks until the desired control or maximal dosage is reached. Sulphonylureas are preferably given 15 to 30 minutes before meals. They can be combined with all other anti-hyperglycaemic agents except glinides and other sulphonylureas. Various clinical trials have failed to conclusively demonstrate superiority of one sulphonylurea over the other, when used in optimal doses. In individual cases, switching from one sulphonylurea to another may show some benefit, but this may not be long lasting.

(a) Factors to be considered when evaluating non-responsiveness to sulphonylureas:

- Weight gain
- Non-compliance to diet and exercise.
- Poor compliance to drugs.

- Inadequate dosage.
- Impaired absorption.
- Co-existing endocrine disorders such as thyroid disease.
- Concomitant medications such as steroids.
- Infections, stress.

(b) Side effects:

Hypoglycaemia is the commonest side effect of sulphonylurea therapy. It is more likely to be prolonged and profound with older and long acting sulphonylureas like glibenclamide and hence they should be used with extreme caution in the elderly. The other side effects are:

- Weight gain
- Photosensitivity reactions (hyperpigmentation of exposed parts) may occur.
- Rarely, skin rashes, leucopenia, anaemia, thrombocytopenia, cholestatic jaundice, Stevens-Johnson syndrome or granulomatous hepatitis may occur.

(c) Contraindications:

- Type 1 diabetes.
- Renal insufficiency.
- Hepatic insufficiency, acute hepatitis.
- Ketoacidosis.
- Acute myocardial infarction.
- Disseminated tuberculosis.
- History of adverse reactions to sulphonylureas.

7.1.3- Dipeptidyl peptidase-4 (DPP-4) inhibitors (Gliptins):

These agents work by inhibiting the enzyme dipeptidyl peptidase-4, which breaks down the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) secreted from the gut in response to a meal. Increase in blood levels of incretin hormones stimulates glucose-dependent insulin secretion from the beta cells of the pancreas and suppression of glucagon release from the alpha cells. The main advantages of gliptins are that they do not cause hypoglycaemia when used as monotherapy and are weight-neutral. Sitagliptin, vildagliptin, saxagliptin, linagliptin, teneligliptin and gemigliptin are the DPP-4 inhibitors available in India at present. Most of the gliptins are used as a single daily dose except vildagliptin which is used twice a day. Gliptins are best used in combination with metformin as second line of therapy. They can also be used as monotherapy or in combination with any other oral antihyperglycaemic agent or insulin. The dosage should be reduced in the presence of renal insufficiency except in the case of linagliptin, teneligliptin and gemigliptin (the latter two to be used with caution in advanced renal disease).

(a) Side effects:

- Gastrointestinal problems – including nausea, diarrhoea and stomach pain
- Flu-like symptoms – headache, runny nose, sore throat.
- Skin reactions – painful skin followed by a red or purple rash.
- Joint pains

(b) Contraindications:

- Acute pancreatitis
- Dose of sitagliptin, vildagliptin and saxagliptin should be reduced in renal impairment, teneligliptin and gemigliptin should be used with caution in advanced renal disease (linagliptin can be continued at unchanged doses)
- Allergic reactions to gliptins.
- Saxagliptin should be avoided in cardiac failure.

7.1.4 SGLT2 Inhibitors (Sodium Glucose Transporter 2 inhibitors):

Canagliflozin, dapagliflozin and empagliflozin are the agents in this class available in India at present. They inhibit SGLT2 located on the proximal convoluted tubule of the kidney thus causing glycosuria. In addition to reducing blood glucose levels, these agents also cause weight loss and reduction of blood pressure. There is also some evidence that these agents have cardiovascular benefits over and above their glucose lowering effects.

(a) Side effects:

- Genital mycotic infections
- Urinary tract infections
- Polyuria
- Volume depletion in elderly persons
- Euglycemic ketoacidosis
- Lower extremity amputations have been reported with canagliflozin

(b) Contraindications:

- Recurrent genitourinary infections
- Patients with diabetic ketoacidosis
- Type 1 diabetes
- Hypersensitivity

7.1.5. Thiazolidinediones (Glitazones):

Pioglitazone is the only agent in this category available in India at present. It is an insulin sensitizer at adipose tissue and skeletal muscle. This effect is brought about by its binding to nuclear peroxisome proliferator activated receptor-gamma (PPAR- γ). It also inhibits hepatic glucose output. Pioglitazone has partial PPAR-

alpha agonist activity, which accounts for its beneficial effects on lipid profile. The dose of pioglitazone commonly used in clinical practice ranges from 7.5 to 30 mg once a day. The action sets in from 2-4 weeks of starting therapy and the maximum effect is observed after 8-12 weeks. Pioglitazone can be combined with all other antihyperglycaemic agents; however, combination with insulin should be done with caution. Women with anovulatory cycles may ovulate when using pioglitazone; hence, adequate contraceptive advice should be given.

(a) Side effects:

- Weight gain may be quite significant and is dose- related.
- Edema and cardiac failure are reported especially when combined with insulin.
- Other adverse events include anaemia and haemodilution.
- Higher risk of fractures especially in post-menopausal women.
- Bladder cancer has been reported on prolonged use.

(b) Contraindications and cautions:

- Type 1 diabetes.
- History of cardiac failure.
- Pregnancy and lactation.
- Moderate to severe anaemia.
- History of bladder cancer or those with unexplained hematuria; known risk factors for bladder cancer to be assessed before starting pioglitazone.
- Use with caution in elderly and avoid use as first-line agent
- Review use after 3 to 6 months and withdraw if clinical benefit not seen

7.1.6 Non-sulphonylurea Insulin Secretagogues (Glinides):

Repaglinide and nateglinide are non-sulphonylurea insulin secretagogues. They are benzoic acid derivatives, which act on separate non-sulphonylurea receptor binding sites on the β -cell and enhance insulin secretion. These agents are absorbed rapidly (0.5-1 hr) and have a short half life (<1 hr). Thus, they result in rapid but brief release of insulin, and hence may be useful in managing postprandial hyperglycaemia. They have to be administered with each meal.

- They produce fewer and milder hypoglycaemic episodes and other side effects compared to sulphonylureas.
- The indications and contraindications for these agents are similar to sulphonylureas.
- They may be used in mild renal insufficiency and elderly under supervision.
- *There is no indication for combining these drugs with sulfonylureas.*

7.1.7 Alpha-glucosidase inhibitors:

Alpha- glucosidase inhibitors (AGI) (acarbose, miglitol and voglibose) act by competitively inhibiting alpha-glucosidase, the enzyme in the small intestine brush border which breaks down oligosaccharides and disaccharides into mono-saccharides. Thus, the absorption of glucose is delayed. AGIs are especially useful in decreasing post-prandial glucose levels. They can be combined with all other oral and injectable anti-hyperglycaemic agents. These agents should be started with the minimum dose at any one meal and then increased to the maximum tolerable dose. They must be ingested with the first bite of food, as the drug must be present in the small bowel with the food for proper effect. Hypoglycaemia rarely occurs if used as monotherapy. If hypoglycaemia results from combination therapy of which AGI is a component, treatment should be with oral glucose rather than sucrose.

(a) Side effects: Gastrointestinal side effects like bloating, abdominal discomfort, diarrhoea and flatulence are common.

(b) Contraindications:

- Inflammatory bowel disease.
- Cirrhosis of liver.
- Malabsorption syndromes.
- Moderate to End Stage Renal Disease

7.1.8 Other oral anti-hyperglycaemic agents:

The disease-modifying antirheumatoid drug hydroxychloroquine and the dopamine agonist bromocriptine are also approved for use as antihyperglycaemic agents in India. The role of these agents in the therapeutic algorithm for type 2 diabetes needs further study. The dual PPAR α / γ agonist saroglitazar is only licensed for use in diabetic dyslipidaemia in India and not as an antihyperglycaemic agent.

7.1.9 General Guidelines for using oral anti-hyperglycaemic agents:

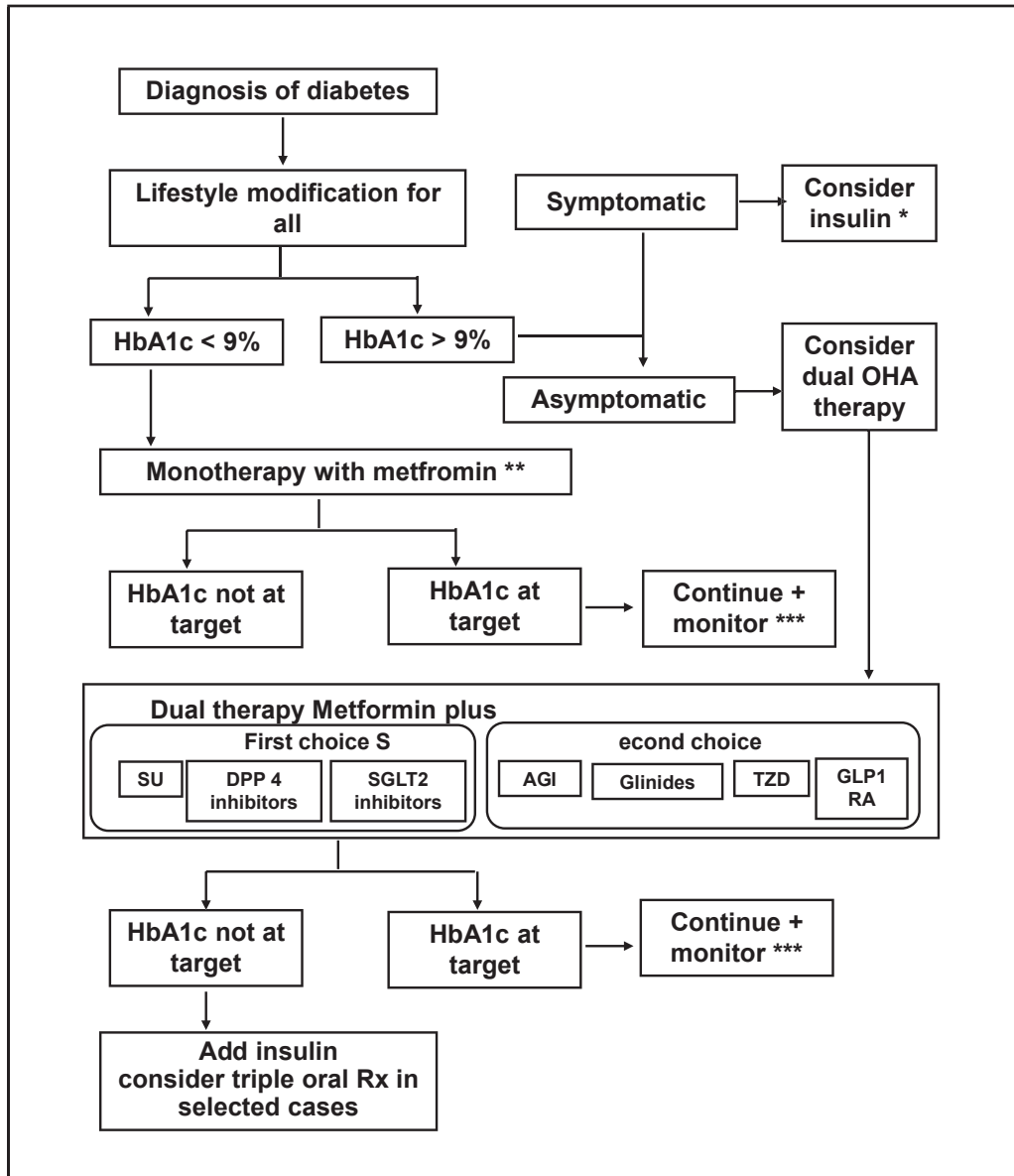
Type 2 diabetes is a heterogeneous disease and hence treatment should be individualized. In every case, due emphasis should be given to encouraging healthy lifestyle choices such as increasing physical activity and modification of diet. In some cases, lifestyle changes alone would suffice to attain therapeutic targets. However, most patients with type 2 diabetes will need pharmacotherapy for achieving their glycemic goals.

To help the practitioner in selecting the optimal antihyperglycaemic agent, we present below a table showing the important advantages and the disadvantages of each class of agent (**Figure 7.2**) and a suggested algorithm for their use (**Figure 7.3**).

Figure 7.2: Pros and cons of various anti-hyperglycaemic agents

AGENT	PROS	CONS
Sulphonylureas	Potent agents Inexpensive	Hypoglycaemia Weight gain
DPP-4 Inhibitors	Low risk of hypoglycaemia Favourable side-effect profile Weight neutral	Expensive
SGLT2 inhibitors	Low risk of hypoglycaemia Reduces body weight and blood pressure	Expensive Risk of genitourinary infection ? Amputation risk
Thiazolidinediones	Low risk of hypoglycaemia Inexpensive	Weight gain Fluid overload Risk of heart failure Fractures
AGIs	Low risk of hypoglycaemia Weight neutral Postprandial glucose regulator	No effect on fasting glucose GI side effects
Glinides	Prandial glucose regulator Lower risk of hypoglycaemia compared to SU	Expensive Less potent No effect on fasting glucose
GLP-1 RAs	Low risk of hypoglycaemia Weight loss	Requires injection GI side effects Expensive

Figure 7.3: Suggested algorithm for use of anti-hyperglycaemic agents



Legend: SU- Sulphonylureas; DPP4i- Dipeptidyl peptidase-4 inhibitors (Gliptins); GLP-1RA- Glucagon-like peptide-1 receptor agonists; TZD- Thiazolidinediones (Glitazones); AGI- Alpha-glucosidase inhibitor; Glinide- Non-sulphonylurea insulin secretagogue (Repaglinide and Nateglinide); SGLT2i- Sodium-glucose cotransporter-2 inhibitor

* with or without oral agents

** If metformin is contraindicated, monotherapy can be initiated with any of the other classes of oral agents

*** Monitor for continued efficacy of drug as well as for development of side-effects

- In practice, majority of patients will require pharmacotherapy at time of diagnosis along with lifestyle modification
- If the initial blood glucose levels are very high, the symptoms are very severe or acute complications like ketosis are present, insulin should be considered even at the onset at least for a brief period for early achievement of euglycemia.
- If the initial assessment shows presence of complications like diabetic retinopathy or nephropathy, this indicates a long period of undiagnosed diabetes and insulin therapy on a continuous basis should be considered.
- With increasing duration of diabetes, most oral anti-hyperglycaemic agents tend to become less effective and hence poly-pharmacy becomes inevitable, with use of drugs from multiple classes. However, insulin use should not be delayed and whenever necessary, insulin should be introduced for tight glycemic control.

7.1.10 Combination of oral drugs with insulin:

When glycemic control is not achieved with the maximum tolerable dose of a single oral agent or combination of oral drugs, combination of oral drugs and insulin can help to achieve good control of diabetes. Oral drugs may be continued in optimal doses, while intermediate acting/long acting/short acting insulin is added either at bedtime or in the morning depending on the blood glucose profile of the patient. When premixed or multiple dose insulin is given, consideration may be given to reducing the dose of secretagogues or stopping them altogether.

7.1.11 Use of Indigenous Drugs:

Many people with diabetes in our country use indigenous drugs from other systems of medicine like Ayurveda, Homeopathy, Unani *etc.* Several herbal products have been advocated for the treatment of diabetes such as *Pterocarpus marsupium*, *Gymnema sylvestre*, *Mormordica chirantica*, *Eugenia jambolana* *etc.* These drugs by themselves or in combination, do have blood glucose lowering effects. Their exact mechanism of action is still not clear. There is a common belief that all herbal drugs are safe and non-toxic which is not necessarily true.

In view of the widespread use of these indigenous medicines, physicians should be aware of the herb-drug interactions. There is ample scope for research and careful evaluation of these agents needs to be done in the management of diabetes.

7.2 Insulin therapy

Insulin is the mainstay of therapy in type 1 diabetes. However, many patients with type 2 diabetes will also require insulin injections to help them achieve their glycemic targets.

7.2.1 Indications for the use of insulin in type 2 diabetes mellitus at the time of diagnosis:

- Person with diabetes with significant, symptomatic hyperglycaemia, loss of weight and polyuria, polydipsia, polyphagia
- Fasting plasma glucose > 270 mg/dl or HbA1c >9%
- Severe infections
- Presence of ketosis

7.2.2 Other situations where insulin is indicated:

- Patients not responding to optimal doses of oral anti-hyperglycaemic agents alone or in combination.
- Acute hyperglycaemia, diabetic ketoacidosis / hyperglycemic-hyperosmolar state / lactic acidosis.
- Stressful situations such as acute myocardial infarction, stroke, acute infections, tuberculosis*,trauma and other conditions requiring hospitalisation
- Pregnancy and lactation.
- Peri-operative state.
- Intolerant / contraindications to OHA.

- Hepatic and renal failure
- Renal transplantation.
- Person with diabetes on steroids.

* Decision left to discretion of treating physician.

7.2.3 Types of insulin preparations:

Different types of insulin are available. They have different pharmacokinetic properties. Insulin type, injection technique, insulin antibodies, site of injection and individual patient response differences can affect the onset, degree and duration of insulin activity.

Human insulin manufactured by rDNA technology and insulin analogues are the only insulins available at present. Animal insulin is no longer available.

(i) Human insulin

- Short acting – human soluble insulin (regular)
- Intermediate acting – neutral protamine Hagedorn (NPH)
- Premixed- mixtures of regular and NPH insulin in 25/75, 30/70, 50/50 proportion

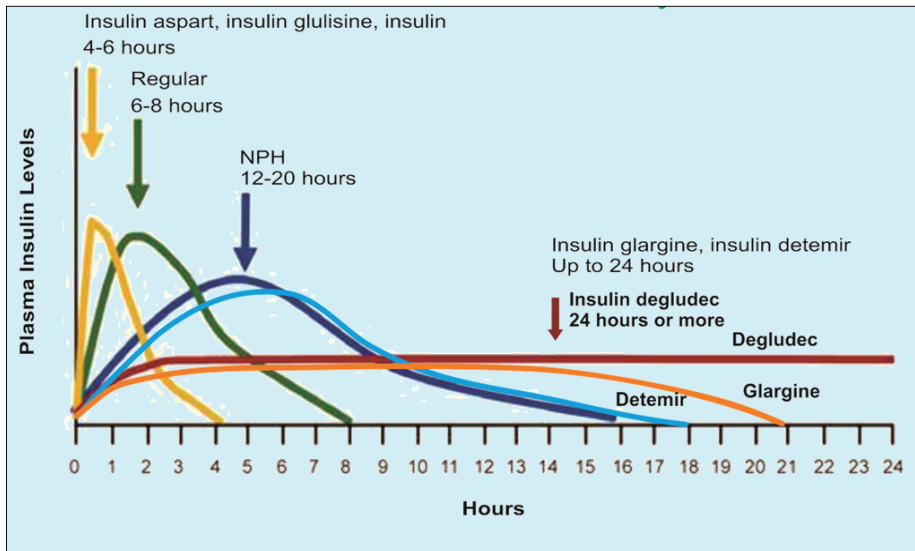
(ii) Insulin Analogues:

- Rapid acting (e.g. Lispro, Aspart, Glulisine)
- Long acting (Glargine, Degludec, Detemir)
- Premixed Insulin analogue (Lispro/ lispro protamine, aspart/ aspart protamine)
- Co-formulations (Degludec + Aspart insulin)

Insulin degludec/insulin aspart (IDegAsp) is a soluble formulation of the novel basal analogue insulin degludec(70%) and insulin aspart (IAsp: 30%)

7.2.4 Insulin action profiles (Figure 7.4):

Figure 7.4: Insulin Profiles After Subcutaneous Injections



7.2.5 Storage of insulin:

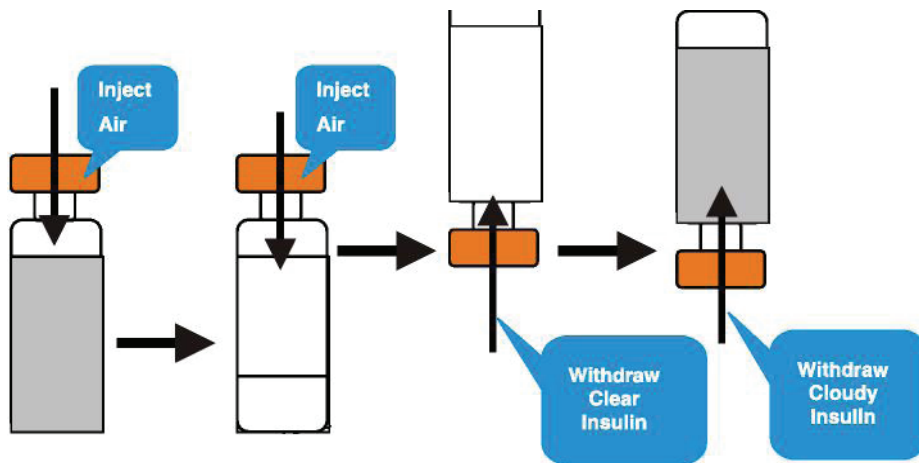
- Insulin not in use should be refrigerated in the lower compartment of the door of the refrigerator. It should not be kept in the freezer compartment. Ideal storage temperature is 2-8° C.
- Insulin should not be exposed to direct sunlight / heat.
- Excess agitation should be avoided to prevent loss of potency, clumping, frosting or precipitation.
- If refrigeration is not available, insulin should be stored in a cool place – e.g., in an earthenware pot of water (inside a plastic bag)
- If regular insulin shows haziness, it should not be used. If cloudy insulin cannot be re-suspended, it should not be used.

7.2.6 Mixing of insulin:

- Administration of mixtures of short and intermediate insulin will produce better glycaemic control than use of single insulin in some patients.
- Regular and NPH insulin can be mixed but must be injected immediately after mixing.

Sequence of mixing insulin is shown in **Figure 7.5**

Figure 7.5: Procedure for mixing insulin



- Before each injection, the hands and the injection site should be cleaned.
- The top of the insulin vial should be wiped with spirit.
- For cloudy insulin preparations (NPH and human and analogue premixes), the vial should be gently rolled in the palms of the hands (not shaken) to re-suspend the insulin.
- An amount of air equal to the dose of insulin required should first be drawn up and injected into the vial to avoid creating a vacuum.
- For a mixed dose, putting sufficient air into both bottles before drawing up the dose is important.
- In case, insulin has to be mixed in the same syringe, (the mixing of rapid or short acting insulin with NPH) the clear rapid or short acting insulin should be drawn into the syringe first.

7.2.7 Use of syringes:

- Conventional insulin administration involves subcutaneous injection with syringes marked in insulin units.
- There may be differences in the way units are indicated (U-40, U-100) and in India, both are available in 1 ml syringe. Fixed needle (single unit) syringes are desirable.
- It is important to make sure that there is no syringe-vial mismatch as far as insulin concentration is concerned e.g. U-40 syringe must be used only for U-40 insulin.
- Syringes and needles must never be shared with another person.
- If reuse is planned, the needle must be carefully recapped after each use. The needle should not be wiped or washed.

7.2.8 Insulin administration:

(i) Insulin pens:

- Several pen-like devices and insulin containing cartridges are available that deliver insulin subcutaneously through a needle.
- They are easy to use.

(ii) Insulin pumps:

- Insulin pump for continuous subcutaneous insulin infusion is available in India with integrated algorithm, which can automatically stop release of insulin thirty minutes before onset of hypoglycemia. It is indicated for those with brittle diabetes, multiple dose injections and recurrent episodes of hypoglycaemia.
- Its use may be restricted to diabetes specialists with relevant experience.

The main problems associated with insulin use are hypoglycaemia and weight gain. Weight gain can be significant and is generally well correlated with the total daily dose of insulin. Used needles must be disposed off in a bio-safe manner. For initiating insulin, it is not necessary to hospitalize the patient. It can be done on outpatient basis.

Insulin colour coding:

Yellow- regular insulin

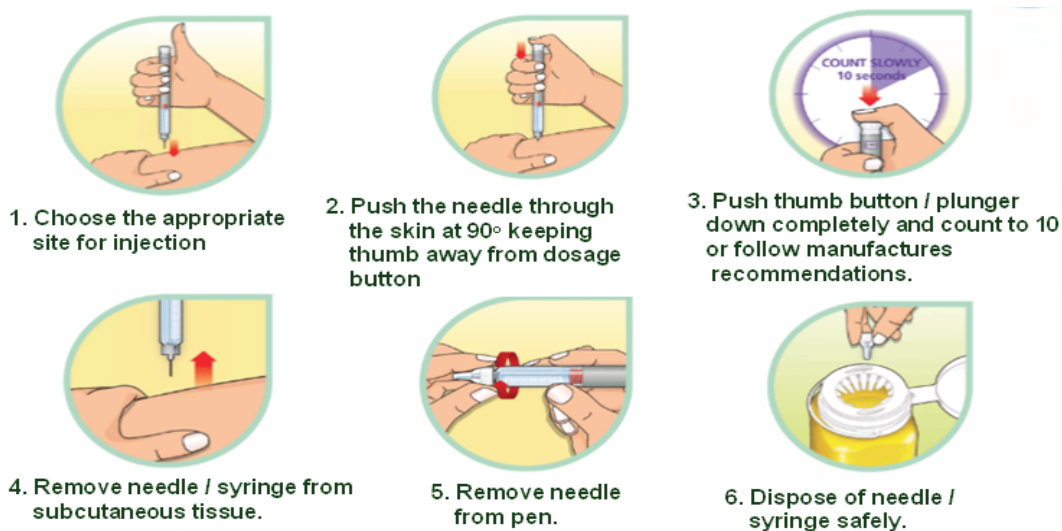
Green- NPH

Brown- Premix insulin

(iii) Injection procedure (Figure 7.6)

- Injections are given into the subcutaneous tissue.
- Inject insulin by lifting up a fold of skin and inject at a 90° angle.
- Thin individuals or children may need to pinch the skin and inject at a 45° angle to avoid intramuscular injection, especially in the thigh area.

Figure 7.6 Procedure for injecting insulin

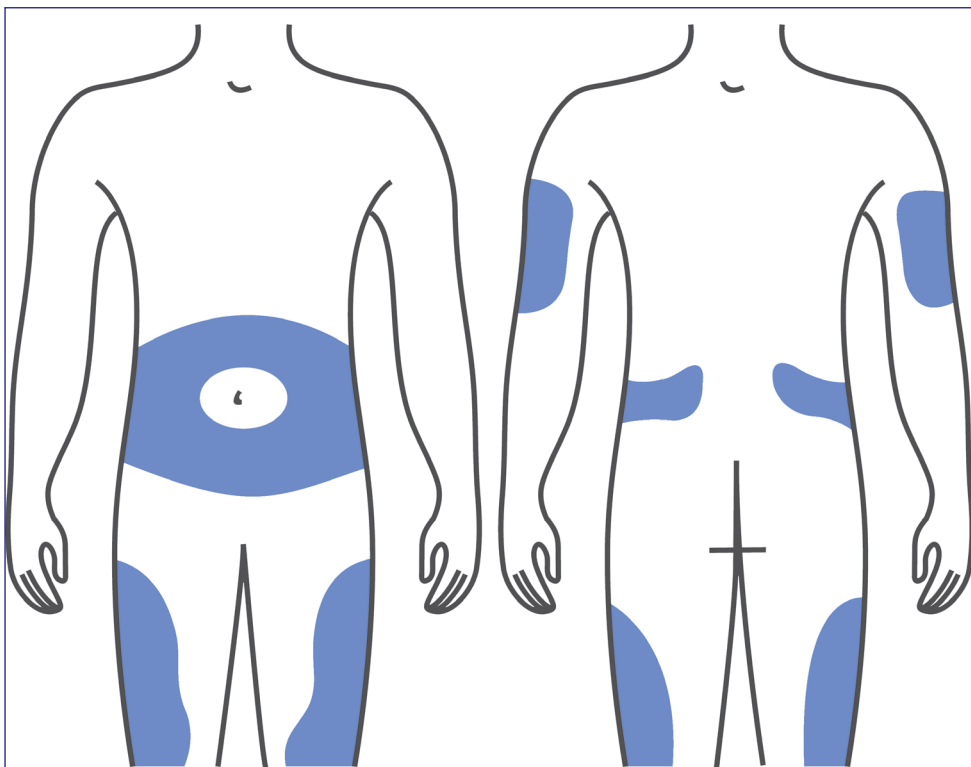


(iv) Injection site

- Insulin may be injected into the subcutaneous tissue of the upper arm, the anterior and lateral aspects of the thigh, the buttocks and the abdomen. For self injection, abdomen and thigh are the convenient sites.

- Rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Rotating within one area is recommended (e.g. rotating injections systematically within the abdomen) rather than rotating to a different area with each injection. This practice may decrease variability in absorption from day to day.
- Site selection should take into consideration the variable absorption between sites. The abdomen has the fastest rate of absorption followed by the arms, thighs and buttocks.
- Exercise increases the rate of absorption from the injection sites.
- The most commonly recommended interval between injection of short acting (regular) / premixed insulin and a meal is 30 min. However, insulin analogues can be given along with or even after a meal.

Figure 7.7 Recommended sites for insulin injection



(v) Adverse effects associated with insulin use:

- The main problems associated with insulin use are hypoglycaemia and weight gain.
- Weight gain can be significant and is generally well correlated with the total daily dose of insulin.

(vi) Disposal of needles:

- Used needles must be disposed of in a bio-safe manner. Used sharps should be collected in a strong cardboard/ glass container, sealed and labelled and handed over to the nearest healthcare facility

(vii) Initiation of insulin:

- For initiating insulin, it is not necessary to hospitalize the patient. It can be done on outpatient basis.
- The dose has to be individualized depending upon the blood glucose profile and clinical setting.
- It is better to start with small doses and modify accordingly every three days.
- Generally, the starting dose of insulin should be 0.2 units/kg/day

(viii) Adding insulin to oral antihyperglycaemic agents:

When combinations of oral antihyperglycaemic agents no longer maintain the level of control desired, insulin is needed (see section 7.1)

(ix) Multiple insulin injections:

- When a single insulin injection plus one or more oral agents no longer maintains good glucose control, two or more injections are needed.
- A regimen containing mixtures of NPH and regular insulin mixed in different ratios (*e.g.* 30:70, 50:50) either mixed by the individual or premixed, taken before breakfast and dinner is a reasonable way to start multiple injections.
- Older persons need careful monitoring to avoid hypoglycaemia.

7.3 Non-insulin injectable therapy (GLP-1 receptor agonists)

The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) are secreted from the gut in response to a meal and bring about glucose-dependent insulin secretion from the beta cells of the pancreas and suppression of glucagon release from the alpha cells. The GLP-1 receptor analogues currently available are resistant to degradation by the DPP-4 enzyme and hence have longer half-lives than native GLP-1. The main advantages of these agents are that they reduce hyperglycaemia with minimal risk of hypoglycaemia and also promote weight loss. The main side effects are nausea and vomiting; a few cases of acute pancreatitis have also been reported. They can be combined with all other classes of anti-hyperglycaemic agents except the DPP-4 inhibitors. There is some evidence that these agents improve cardiovascular outcomes over and beyond their effects on blood glucose. Exenatide, liraglutide, lixisenatide and dulaglutide are the GLP-1 receptor agonists available in India at present (Table 7.2).

Table 7.2. GLP - 1 Receptor Agonists

Drug name	Daily dosage	Frequency per day	Duration of action (hrs)	Mode of excretion
Exenatide	5 - 20 mcg	2	10	Urine
Liraglutide	0.6 - 1.8 mg	1	24	Endogenous metabolism without major organ excretion
Lixisenatide	10 - 20 mcg	1	24	Urine
Dulaglutide	0.75 - 1.5 mg	Once per week	24 - 72	Endogenous metabolism, degraded to smaller proteins and amino acids

Most of the morbidity and mortality due to diabetes arises on account of its complications. Diabetes complications can be broadly divided into acute and chronic complications. Acute complications include hypo- and hyperglycaemic emergencies whereas chronic complications include microvascular disease (retinopathy, nephropathy and neuropathy), macrovascular disease (coronary artery disease, cerebrovascular disease and peripheral vascular disease) and diabetic foot.

8.1 Acute complications

8.1.1 Hypoglycaemia:

It is a common side effect due to drug therapy of diabetes especially sulphonylureas and insulin. The patient may have classical symptoms like hunger, sweating, tremors, palpitation with or without loss of consciousness.

Steps to be taken:

- If glucose monitor is available, random plasma glucose should be estimated.
- If glucose monitor is not available and patient is conscious, he should be treated with oral glucose/ sweets/sugar.
- If patient is brought in unconscious state, give 25-50 ml of 25% dextrose IV
- If there is inadequate response, maintain a 5% dextrose drip and refer to hospital immediately.
- If recurrent hypoglycaemia persists, check for renal function and hypothyroidism.

8.1.2 Hyperglycaemic emergencies (Diabetic Ketoacidosis- DKA or Hyperosmolar Hyperglycaemic State- HHS):

Usually such emergencies occur in situations like infections or other stressful conditions. There is usual history of missed dose of insulin or poor control of diabetes. DKA is characterized by abdominal pain and is manifested with breathlessness, vomiting, altered sensorium and dehydration. The symptoms of HHS are predominantly neurological; dehydration is usually more profound but abdominal pain is uncommon.

Steps to be taken:

- Monitor glucose levels.
- Check for urine ketones
- Intravenous saline infusion at 1 litre in half hour should be started immediately and refer to hospital.

8.2 Chronic Complications

Diabetes mellitus is a systemic disorder, which potentially can cause serious organ damage involving eyes, heart, kidney, nerves and limbs, which ultimately can lead to blindness, heart attack, kidney failure and limb amputation respectively. If diagnosed early and treated in time appropriately, the damage to some of these organs can be largely prevented or reversed. Another important issue is that most complications cause clinical symptoms only at a very late stage and thus for their early diagnosis, these complications have to be specifically looked for even at the time of prediabetes. Considering this, the following approach is advisable for management of people with type 2 diabetes.

On the first clinic visit detailed history and a thorough examination with preliminary tests are essential. Additional investigations may be necessary if there are high risk factors in the patient and/or there is any abnormality in history, examination and preliminary investigations. At that stage, these patients need to be referred to specialists for further management.

8.2.1 History

8.2.1.1 Present history:

- Has the patient any specific symptoms related to organ involvement that have brought him/her to the doctor?
- Duration of diabetes
- Medications and doses
- Compliance with medication and life style measures
- Latest blood glucose, HbA1C and other lab reports available

8..2.1.2 Past history:

- Hypertension
- Heart disease
- Known kidney disease
- Tuberculosis
- Eye problem including history of laser treatment / therapy
- Surgery, past history of non-healing ulcer and / or amputation

8.2.1.3 Personal history:

- Smoking and tobacco use
- Alcohol intake
- Dietary habits include intake of non vegetarian foods
- Exercise regimen

8.2.1.4 Family history:

- Diabetes and diabetic complications
- Hypertension
- Kidney diseases
- Stroke

- Coronary artery disease

8.2.2 Examination:

- Blood pressure (sitting and standing)
- CVS examination-heart sounds, murmurs
- Other systemic examinations - respiratory, neurology, abdomen, musculoskeletal etc.
- Peripheral pulses/carotid pulses
- Pedal edema
- Complete foot examination (ref page 45)

8.2.2.1 Eye examination:

- Visual acuity
- Intra Ocular Pressure (if possible)
- Retinal examination including fundus examination after dilatation (ophthalmoscopy)
- Cataract

8.2.3 Investigations:

- These are detailed under each complication
- In selected cases, X-ray chest may also be indicated

8.3 Coronary Artery Disease

- When patient is asymptomatic with abnormal E.C.G, refer to specialist / physician / cardiologist.
- If the symptoms suggest suspicion of unstable angina / acute myocardial infarction MI, give aspirin and statin, refer to nearest hospital urgently.

8.4 Diabetic Nephropathy

8.4.1 Investigations:

- Urine microscopy (Casts and pus cells, RBC)
- Blood Urea, Serum creatinine

- Microalbuminuria
- USG abdomen (if feasible)
- Serum sodium and potassium

8.4.2 Management of albuminuria /proteinuria:

The algorithm given in the next page outlines the steps in investigation of albuminuria / proteinuria in a person with diabetes.

8.4.3 Treatment of hypertension in nephropathy:

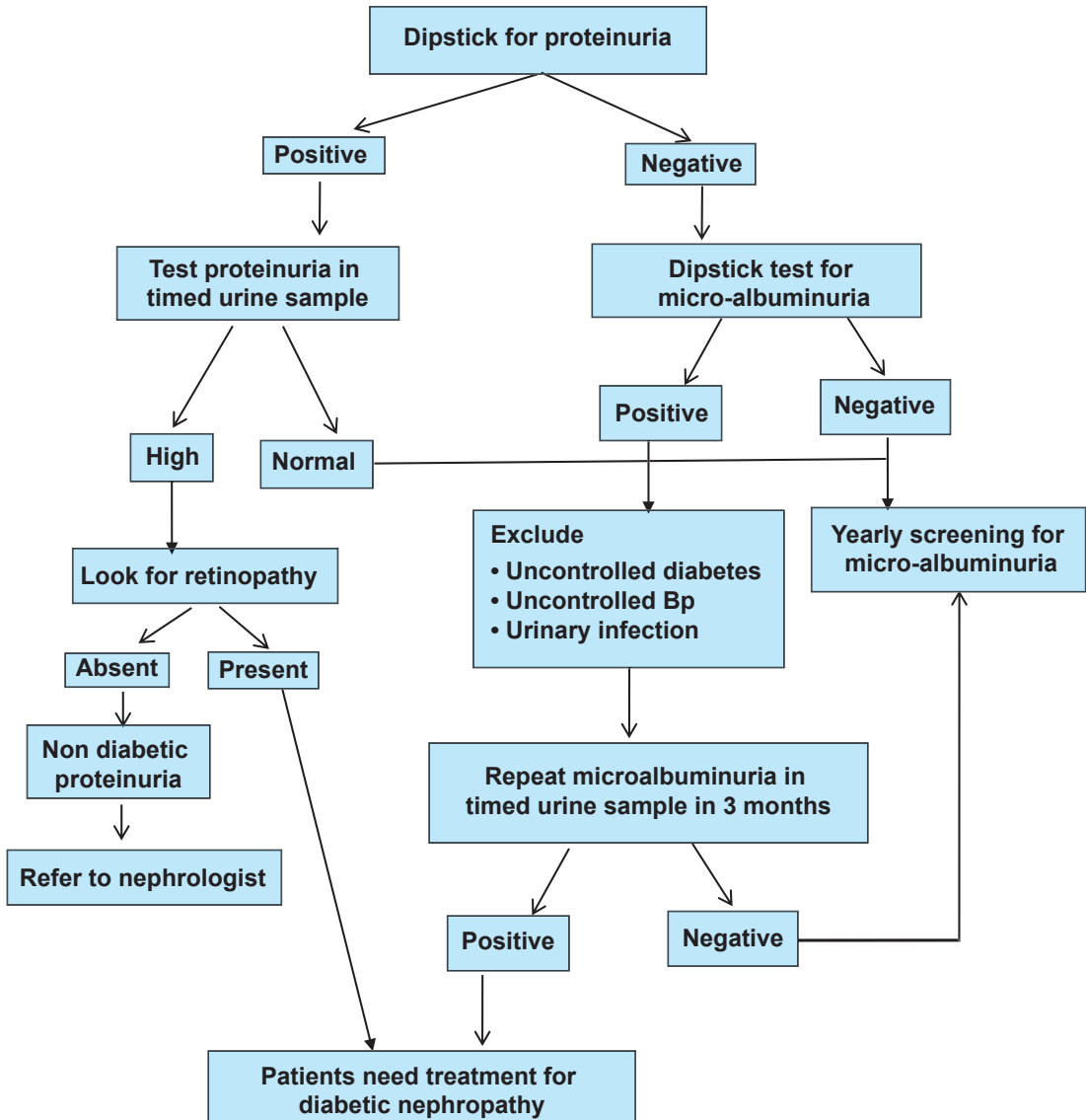
- Angiotensin converting enzyme (ACE) inhibitors or Angiotensin II receptor blockers (ARB) are the drugs of choice (never combine both)
- Others, if ACEIs or ARBs are not tolerated.
- Calcium channel blockers
- Diuretics.
- Selective beta blockers (should be given in case of known previous acute coronary syndrome).

8.4.4 Refer the patient to nephrologist if:

- Patient has severe/resistant hypertension
- Patient has serum potassium > 5.5 meq/L
- Patient has nephrotic range proteinuria
- Proteinuria is present in absence of retinopathy.
- Serum creatinine is > 1.5 mg%.
- Any patient with pregestational diabetes or GDM with proteinuria
- eGFR as calculated by MDRD is < 60 ml/min.
- Presence of fluid overload or oliguria.

Figure. 8.1 shows a suggested algorithm for the evaluation of proteinuria in a patient with diabetes. This will help differentiate proteinuria of diabetic and non-diabetic etiology.

Figure 8.1: Algorithm for evaluation of non-diabetic proteinuria



Diabetic Retinopathy:

Ninety percent of blindness from diabetic retinopathy (DR) is preventable by early diagnosis and treatment. All physicians dealing with diabetic retinopathy patients in large numbers must make an effort at recording visual acuity as an integral part of their work up and must strive to develop the skill of direct ophthalmoscopy. If visual acuity recording and retinal examination is not possible, all physicians must spend time educating their diabetic patients on the strong potential for diabetes to cause blindness, about how this can be prevented by regular visit to a retina specialist and about the need for an immediate baseline eye examination and blood glucose control. Recording of visual acuity and examination of the retina by ophthalmoscopy is mandatory in all diabetic patients. Whenever possible retinal photography must be obtained. If the services of a retina specialist are available, his / her opinion should be sought about the stage of retinopathy, any need for immediate / early treatment and about the next follow up visit. If services of a retina specialist are not available, then it is advised to compare retinal examination findings and/or findings on retinal photography with representative diabetic retinopathy images and corresponding management/ follow up guidelines or refer to the grades of diabetic retinopathy chart and advise patients accordingly.

- Those patients who have a long history of diabetes, poor glycemic control, concurrent hypertension and nephropathy are more likely to have diabetic retinopathy.
- Pregnant women with diabetes also need frequent retinal examination as pregnancy may accelerate the development and progression of retinopathy.
- Visual acuity may be normal despite having diabetic retinopathy.
- However, when the visual acuity is found to be decreased in any patient with diabetes mellitus, it must be considered to be due to vision threatening diabetic retinopathy and the patient must be referred immediately to a retina specialist.

8.5.1 Risk factors:

- Long duration of diabetes
- Poor glycemic control
- Uncontrolled hypertension
- Presence of diabetic nephropathy

8.5.2 General considerations:

- Inform all patients that sight threatening eye disease is a common complication of diabetes.
- Severe diabetic retinopathy can be present even with good vision.
- Glasses testing/refraction should not be mistaken for retinal examination.
- Physicians should impress that it is mandatory to undergo a dilated retinal examination preferably by a trained retina specialist.
- Vision testing and (if possible) intraocular pressure testing should be done before retinal examination in all patients.
- Person with impaired vision (< 6/60) should undergo low vision evaluation and rehabilitation.
- Person with diabetes should be screened for other causes of visual loss like cataract, glaucoma and macular degeneration.

8.5.3 Screening recommendation for retinal examination *:

Patient Group	When to screen first	Routine follow-up
Type 1 diabetes	Within 5 years of diagnosis	Annually thereafter
Type 2 diabetes	At time of diagnosis	Annually thereafter
Pregnancy in pre-existing diabetes, retinal examination prior to conception and during pregnancy, refer to the ophthalmologist / -retina specialist early in the first trimester		

* Based on the findings during the fundus examination, subsequent follow up advice is provided.

8.6 Diabetic Neuropathy

8.6.1 *Diagnosis & clinical recognition:*

- Sensory neuropathy is evidenced by symptoms of paresthesiae (such as tingling, numbness and pain) or loss of sensation of touch, pain, temperature and vibration.
- Neuropathy can lead to foot deformities and dryness of plantar skin leading to neuropathic foot ulcers. These ulcers are susceptible for infection, cellulitis and osteomyelitis often requiring partial foot amputation.
- Motor weakness of small muscles of foot is evidenced by inability to grip footwear and alteration of arch of foot, bringing pressure on the head of first metatarsal and heel.
- Quadriceps wasting and absent knee jerk and bilateral hip muscle weakness suggests diabetic amyotrophy.
- Cranial motor neuropathy involving 3rd, 6th and rarely 7th nerve must be considered in relevant cases.
- Radiculopathy and cranial neuropathies are reversible while sensorimotor symmetrical polyneuropathy is progressive and irreversible.
- Assess for autonomic neuropathy with symptoms such as orthostatic hypotension, gastroparesis, diarrhoea /constipation, impotence, cystopathy and gustatory sweating.
- Always exclude other causes of neuropathy for example nutritional deficiency, hypothyroidism, spinal disorders, paraneoplastic syndrome, drug induced, alcohol abuse, uremic neuropathies, etc.

8.6.2 *Clinical examination:*

- For sensation as described under foot examination
- Motor power assessment and tendon jerks
- Examination of BP in sitting and standing positions and ECG for heart rate variability may be useful in diagnosing autonomic neuropathy.

8.6.3 Investigations:

- TSH
- Vitamin B12 assay (if possible)
- Paraproteinemias (if possible)

Refer to a neurologist for atypical cases for further investigations like nerve conduction studies etc.

8.6.4 Treatment:

- Tight glycemic control is essential. If there is painful peripheral neuropathy, drugs such as antiepileptics (gabapentin, pregabalin), tricyclic antidepressants (TCAs) (amitryptiline, imipramine), and serotonin and noradrenaline reuptake inhibitors (SNRIs), (venlafaxine, duloxetine) are the first line medications. Either the maximum dose of each drug or a combination of two drugs must be tried to give relief. In resistant painful neuropathies use of second line drugs like use of opioids (tramadol) is also advised.
- If patient has symptoms and signs of numbness and loss of sensations, follow the guideline given under foot care to protect the foot from ulceration.
- Sexual dysfunction in males should be referred to specialists for appropriate therapy.

8.7 Diabetic Foot

8.7.1 Diabetic foot screening:

This aims at categorizing feet into Low risk, At Risk or Active Foot Disease. Examination of a patient should include:

8.7.1.1. Foot inspection:

- Inspection of skin, nails and for structural foot deformity.
- Examination of footwear.
- Record presence of:

- toe deformities like claw toes, hammer toe
- bunion
- high arch foot (pes cavus)
- Charcot foot

8.7.1.2. 10g monofilament sensation:

It delivers a 10 gram force when applied so as to make it buckle. A person who can feel the 10 gram filament in the selected sites (**Figure 8.2.C**) is at reduced risk for developing ulcers.

- Apply the monofilament perpendicular to the skin's surface (see **Figure 8.2.A** below).
- Apply sufficient force to cause the filament to bend or buckle (see **Figure 8.2.B** below).
- The total duration of the approach, skin contact, and departure of the filament should be approximately 1- 2 seconds.
- Apply the filament along the perimeter and NOT ON an ulcer site, callus, scar or necrotic tissue. Do not allow the filament to slide across the skin or make repetitive contact at the test site.

Figure 8.2. The monofilament test

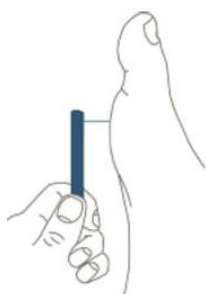


Figure 8.2.A

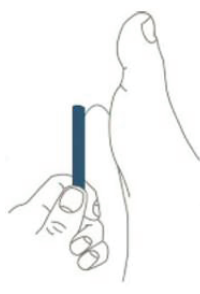


Figure 8.2.B

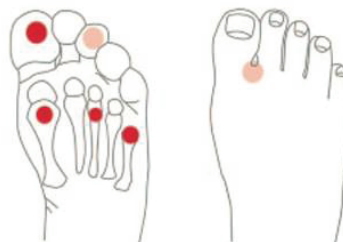


Figure 8.2.C

8.7.1.3. Vibration perception (128 Hz tuning fork):

Place the stem of the fork over the bony prominences of the foot (big toe and medial malleolus) and ask the patient if he feels the vibration. Record the result as absent, reduced or present depending on the patient's response. If absent, check at more proximal sites such as tibial tuberosity and anterior superior iliac spine.

8.7.1.4. Biothesiometer test:

The vibration perception threshold (VPT) is examined using a biothesiometer with the patient in the supine position with or without eyes closed.

8.7.1.5. Vascular assessment:

This involves the manual palpation of the dorsalis pedis and posterior tibial pulses in both feet. Ankle brachial pressure index (ABI) using hand held Doppler should be assessed if peripheral pulsations are absent or clinical suspicion of peripheral ischaemia (Normal ABI is between 0.9 to 1.3).

8.7.2. Risk categorization:

Risk categorization method for basic foot screening involves history of diabetes-related foot complications, medical history, and assessment of peripheral sensation, arterial supply and presence of foot deformity (**Table 8.1**)

Table 8.1 Risk categories in diabetic foot

Risk Category	Clinical Features	Frequency of assessment	Examiner
Low risk	Normal foot pulses, normal vibration and sensation to 10g monofilament, no history of foot ulceration, no significant foot deformity, no visual impairment.	Annual	Foot healthcare provider
Moderate risk	Reduction in vibration and monofilament sensation and/or absence of pedal pulses	Annual or more frequently as required	GP/foot health care provider, podiatrist and physiotherapist
High risk	Claudication / rest pain History of ulceration / Charcot neuroarthropathy	Every 6 months or more frequently as required	GP/ foot health care provider, podiatrist and physiotherapist
Active foot disease	Ulceration, infection, suspicion of Charcot foot or ischaemia	At least once weekly or more frequently as required	Diabetes multidisciplinary footcare service

(Note: those with previous history of foot ulcer, amputation or PVD need foot examination at every clinic visit or at least every 3 months)

8.7.3. General Principles of Management:

- There is no need for a patient with low risk of diabetic foot disease to routinely see a podiatrist / physiotherapist for diabetes related purposes.
- All patients with diabetes should receive foot care education (See Do's and Don'ts below-**Table 8.2**)
- Risk factors like tobacco use should be controlled in every case
- Patients with foot deformity that interferes with the function of the foot or the ability to obtain appropriate footwear should be referred for specialist assessment.
- Similarly, patients with absent pedal pulses should be referred for vascular assessment.
- If ulceration is present then refer within 24 hours to multidisciplinary foot care service.
- If there are clinical signs of infection, antibiotics should be commenced immediately. If there are clinical signs of severe/limb threatening infection, the patient should be admitted urgently for intravenous antibiotic therapy and surgical debridement or referred to appropriate higher centres.

8.7.4. Foot care education:

All patients with diabetes should be educated on the do's and don'ts of foot care as listed in the **Table 8.2** below.

Table 8.2: Foot care — Do's and Don'ts for patients

Do	Do not
Inspect feet daily using mirror	Walk barefoot
Wash feet daily in lukewarm water, also in between toes	Do not Smoke/alcohol abuse
Apply moisturizing lotion to feet after drying	Expose to extreme temperature
Have your feet checked at each clinic visit	Use hot fomentation
Inspect footwear daily for defects/foreign bodies	Use chemicals agents (e.g. corn plaster), corn caps or blades to treat corns or calluses
Change footwear regularly	Wear new footwear for more than few hours
Buy footwear preferably in the evening	Neglect any minor foot lesions

SECTION 9 DIABETES AND PREGNANCY

9.1. Pre-gestational diabetes

Women with pre-existing diabetes, (e.g. type 2 or type 1 diabetes) who become pregnant are said to have pre-gestational diabetes. Maternal and fetal outcomes are good if the pregnancy is planned and tight glycaemic control is achieved. The steps to achieve these are:

- Tight glycaemic control (preferably HbA1C (< 6.5%)) is ideal before a planned pregnancy.
- Folic acid supplementation should be given.
- Antihypertensive agents should be changed to calcium channel blockers or alpha methyl dopa.
- ACEIs, ARBs, Diuretics and Statins should be discontinued
- Pre-pregnancy baseline evaluation of eyes and kidney function must be done.
- Optimisation of nutritional status, anaemia and pre-pregnancy weight should be done.
- Maternal and fetal surveillance during pregnancy should ideally be done by an obstetrician and physician.

9.2 Gestational Diabetes Mellitus (GDM)

Glucose intolerance of any severity detected for the first time during pregnancy is termed as gestational diabetes mellitus (GDM).

9.2.1 Screening for gestational diabetes:

9.2.1a Indications:

Ideally *all* pregnant women in India should be screened for GDM i.e. universal screening. In case this is not possible, and only selective screening is done, at least the following women should be screened:

- History of GDM.
- First degree relative with diabetes
- Pre-pregnancy obesity (BMI > 25 kg/m²)
- History of large weight babies (>3.5kgs)
- Bad obstetric history; - stillbirth, congenital anomalies, recurrent pregnancy loss, , eclampsia, hydramnios
- Repeated or persistent urinary tract infection.
- Glycosuria during pregnancy.
- Age above 25 years.

However, if all these criteria are employed there will be very few women who are at low risk and do not need screening for GDM. Hence, it is better to try to screen all pregnant women for GDM.

9.2.1b Screening methods for GDM:

Screening for diabetes is ideally done at the first antenatal visit. Screening at the first trimester is mainly to rule out pre-existing diabetes. For this, fasting blood glucose or random blood glucose or HbA1C should be done. If the fasting glucose is ≥ 126 mg/dl or the random glucose is ≥ 200 mg/dl or HbA1C is $\geq 6.5\%$, it indicates pre-existing diabetes. A fasting plasma glucose between 92-125 mgs/dl at the first trimester screening is considered as GDM according to International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. At the second trimester,

screening for GDM is done usually between 24 and 28 weeks of gestation. An Oral Glucose Tolerance Test (OGTT) should be done using 75 gm glucose load using the IADPSG criteria (endorsed by WHO 2013 & FIGO 2016). The following are the IADPSG glucose cut-offs for GDM:

Fasting Plasma Glucose (mg/dl)	≥ 92
1 hour (mg/dl)	≥ 180
2 hour (mg/dl)	≥ 153

If any one of the values is above these cut-offs, the woman is diagnosed to have GDM.

In situations where pregnant women cannot come in a fasting state and in resource limited settings, the Diabetes in Pregnancy Study Groups of India (DIPSI) guidelines of non-fasting 75 gms single 2 Hr post glucose value ≥ 140 mg/dl can be used.

9.3. Management of hyperglycaemia in pregnancy

Insulin is the preferred drug of choice in diabetes and pregnancy. Currently most types of insulin are approved for use in pregnancy except Glargine, Glulisine and Degludec.

Increasingly studies are showing the safety of Metformin in pregnancy.

Besides glycemic control, fetal growth and maternal blood pressure need to be monitored.

9.3.1 Goals for therapy:

Fasting Plasma Glucose (mg/dl)	<90
1 hour Postprandial Glucose (mg/dl)	<140
2 hour Postprandial Glucose (mg/dl)	<120

9.4 Post-partum follow up

As 50-70% of women with GDM go on to develop diabetes within 5-10 years after delivery, post partum screening for diabetes is necessary. A 2 hr OGTT using 75g glucose should be done 6-8 weeks after delivery for reclassification of diabetes as normal, pre-diabetes or diabetes. If normal, the testing should be repeated annually.

10.1 Hypertension

Hypertension in patient with diabetes more than doubles the risk of morbidity and mortality from strokes and heart attacks. It is also one of the important correctable factors for reducing the risk of diabetic nephropathy. Hence it is essential that blood pressure should be checked on every visit and kept under control. A blood pressure (BP) more than 140/90 mm is the trigger to initiate treatment. Initial attempt should be made to control the BP by non-pharmacological measures. These include weight reduction, dietary modification by reducing salt intake and stress management (if possible).

A person with diabetes as well as with hypertension should be treated more aggressively than an individual with hypertension but without diabetes.

10.1.1 Blood pressure management and targets:

If blood pressure is >140/90mm Hg
Recheck after 1 week

If still high, drug therapy needs to be initiated with a single drug

1. ACE inhibitors /ARB (do not combine both) (or)
2. Calcium channel blockers
3. Selective beta blockers or diuretics (as a third line option if indicated)

If the blood pressure remains >140/90 mm Hg after 1 month of monotherapy, add a second drug from a different class (do not combine ACEI and ARB). If BP is not controlled even with optimal doses of two agents, referral to a specialist is indicated. In patients with diabetic renal disease, even lower BP targets are recommended.

10.1.2 Severe hypertension:

If at initial visit, blood pressure is > 180/110 mm Hg, or the patient has evidence of end organ damage, treatment should be initiated with two drugs initially and patient should be referred to a specialist as early as possible.

10.2. Dyslipidaemia

All patients with diabetes should be screened for dyslipidaemia and if present should be treated aggressively

10.3. Obesity

Weight reduction should be attempted in obese individuals. Lifestyle modification is the main stay of treatment and judiciously drugs may be used as an adjuvant. In morbid obesity, bariatric surgery may be an option.

10.4 Tuberculosis

Tuberculosis (TB) is one of the major public health problems in India. The prevalence of diabetes is high among people with TB in India and about 25% of TB patients were found to have diabetes and 24%, pre-diabetes. Diabetes is believed to elevate the risk of contracting TB by 2.5 to 3-fold. There should be a high index of suspicion for TB in all patients with diabetes. Wherever clinically indicated, initial evaluation of a patient with diabetes should include a chest X-ray.

Reducing morbidity and mortality due to TB and DM can be achieved through integrated approach of prevention, bidirectional screening for early detection in routine health care setting and management strategies through integration of services for TB and diabetes. Insulin is preferred if diabetes is uncontrolled or the TB is severe.